REMARKS

Claims 1-3, 5-8, 10, 11, 13, 14, 16-20, 26 and 81-85 presently appear in this case. No claims have been allowed. Claims 17-20 have been withdrawn from consideration. The Official Action of April 12, 2011, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a lipid assembly, being an organized collection of lipids, the lipids of which consist of at least one biologically active non-liposome forming lipid, a lipopolymer, and at least one liposome forming lipid. The biologically active non-liposome forming lipid has a hydrophobic region and a polymer headgroup wherein the atomic mass ratio between the head group and the hydrophobic region is less than 0.3. The lipopolymer has a hydrophobic lipid region and a hydrophilic polymer headgroup and a atomic mass ratio between the head group and the hydrophobic region is at least 1.5. The components of the lipid assembly are selected such that the lipid assembly is chemically and physically stable under storage conditions of 4°C in biological fluids for at least six months. The invention also relates to a pharmaceutical composition comprising the lipid assembly and a physiologically acceptable carrier. The lipid assembly is

present in an amount sufficient to achieve a biological effect at a target site.

Claims 1-3, 5-8, 10, 11, 13, 14, 16 and 26 have been rejected under 35 USC 112, second paragraph, as being indefinite. The examiner states that the requirement that the lipid assembly be chemically and physically stable is indefinite as it is unclear what is meant by "stable." The examiner states that the specification does not state which pH ranges would be considered stable, what levels of hydrolysis are considered stable, what sizes of aggregates are considered stable and how much free lipid is permitted for the composition to be considered stable. This rejection is respectfully traversed.

Any person familiar with the recited tests would know, based on conventional statistical analyses, how to determine whether a change (based on these tests) from freshly made liposomes is considered significant to an extent that would lead to the conclusion that the liposomes are unstable. In this connection, please note the following:

Chemical test (a): which is conducted with a pH meter. The examiner argues that applicant does not specify which pH ranges are considered stable and which unstable. However, a person versed in the art would readily understand

that the use of a pH meter is for determining that there is no significant change in the pH of the system from the pH of freshly prepared liposomes. In the particular examples, the initial liposomal pH of all freshly prepared liposomal formulations was about 7.0 (physiological pH). During storage at 4°C, follow-up studies of the liposomal pH were conducted by measuring their pH, and it was found to essentially remain in the same range. See paragraph [0283] of the published copy of the present specification:

> The results indicate that when stored at 4° C. in citrate buffer, pH 7. 0 all liposome formulations were chemically stable for at least 6 months as the level of NEFA did not increase above 3%.

Thus, those of ordinary skill in the art would understand that any significant change from physiological pH is a sign of instability.

Chemical stability test (b): involving phospholipid acylester hydrolysis. The examiner argues that applicant does not disclose what levels of hydrolysis are considered sufficiently stable and what are not. However, as with pH, a person skilled in the art would readily understand that a stable liposome is such with minimal hydrolysis. In the above-quoted example, the NEFA, which is released upon PL hydrolysis, did not increase above 3%.

This was considered stable. Any amount of NEFA significantly above 3% would be evidence of instability.

Physical stability test (a): involving assembly size distribution conducted by dynamic light scattering (DLS). The examiner argues that applicant does not disclose which sizes are considered stable. However, a person versed in the art, being familiar with the DLS test, would readily appreciate that the lack of aggregate formation over time, would suffice to determine stability according to this test, particularly in view of the comment in paragraph [0115]-[0116]:

> … typically resulted in unstable systems having a tendency to aggregate and/or phase separate, and/or the substances spontaneously leaked out the non-liposomal forming substance upon storage.
>
> Based on the results presented herein, it has now been established that by combining lipids which do not spontaneously form liposomes with an amount of a lipopolymer it is possible to obtain stable (during long term storage at 4° C.) incorporation of such lipids into stable lipid assemblies. These lipid assemblies did not aggregate, do not exhibit a change in their size or in ceramide content during storage for long periods of time (> 1 year). [Emphasis added.]

In this connection, it is noted that it does not matter what is the size of the fresh liposomes. They may be in the size range of 50-150 nm or even larger (see paragraph [0154]. Against this instable liposomes were considered as a

substantial increase in size, due to the formation of aggregates (see TABLE 6 of the present specification). A substantial decrease in size could also evidence leakage of the ceramide (see paragraph [0115]). Such differences would readily be understood by a person versed in the art as any significant change in size would be indicative of instability.

Physical stability test (b): involving TLC. The examiner argues that applicant does not disclose what level of free ceramide is required to define lack of stability. Again, a person versed in the art would readily understand how to employ TLC test to determine presence of free ceramide, and that any substantial release of ceramide is indicative of instability of the liposome.

In view of the above, those of ordinary skill in the art would consider the terms used to be sufficiently definite to at least meet the threshold requirements for clarity and precision. The examiner's attention is invited to MPEP 2173.02, where it states:

> When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted

> even though the claim language is not as precise as the examiner might desire. [Emphasis original.]

Here, the present amendments should obviate all of the art rejections, so that this will be the only remaining ground of rejection. As the claims define the patentable subject matter with a reasonable degree of particularity and distinctness, for the reasons discussed above, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1-3 10, 11, 13, 14 and 16 have been rejected under 35 USC 102(b) as being anticipated by Needham, as evidenced by Israelachvili, Kumar and Tirosh. This rejection is respectfully traversed.

It is noted that claim 5 was not included in this rejection. The subject matter of claim 5 has now been inserted into claim 1. Accordingly, claim 1, and those claims dependent therefrom, are now free of anticipation for the same reason that previously appearing claim 5 was free of this rejection. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 5 and 26 have been rejected under 35 USC 103(a) as being unpatentable over Needham. The examiner states that Needham suggests the inclusion of ceramide at

column 5, line 60. This rejection is respectfully traversed.

Claim 1 has now been amended so as to exclude the presence of lysolipid, which is the critical component of Needham. Claim 1 now defines the lipids of the lipid assembly as "consisting of" the various lipid components. The at least one biologically active non-liposome forming lipid is now defined by a Markush group that does not include lysolipid. As no lipid other than (a), (b) and (c) of claim 1 can be present, Needham cannot anticipate. In the composition of Needham, lysolipid must always be present. As it is excluded by the present claims, it cannot be obvious from Needham. Nobody of ordinary skill reading Needham would have any reason to eliminate the lysolipid. Accordingly, this rejection has now been obviated. Reconsideration and withdrawal thereof is respectfully urged.

Claims 5-7 have been rejected under 35 USC 103(a) as being unpatentable over Needham in view of Wei. The examiner states that Wei teaches a liposome comprising phosphatidylcholine, cholesterol and either C2-ceramide or C6-ceramide. Thus, the examiner considers it obvious to have included C2 or C6 ceramide in the liposome of Needham. This rejection is respectfully traversed.

As indicated above, claim 1 has now been amended to exclude the presence of lysolipid. Wei provides no motivation to remove lysolipid from the composition of Needham, particularly as Needham considers this to be a critical component. Accordingly, no combination of Needham with Wei can make obvious the presently amended claims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 6 and 8 have been rejected under 35 USC 103(a) as being unpatentable over Needham in view of Igarashi. The examiner states that Igarishi teaches the effect of N,N-dimethylsphingosine and N,N,Ntrimethylsphingosine against cancer cells. Thus, the examiner considers it obvious to have included these sphingosines in the liposome of Needham. This rejection is respectfully traversed.

As indicated above, claim 1 has now been amended to exclude the presence of lysolipid. Igarashi provides no motivation to remove lysolipid from the composition of Needham, particularly as Needham considers this to be a critical component. Accordingly, no combination of Needham with Igarashi can make obvious the presently amended claims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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